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A monthly update of developments in cancer treatment and research [ALERT]

ABSTRACT & COMMENTARY

Oral Sapacitabine for Treating Elderly Patients with AML

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Dr. Prabhakar reports no financial relationships relevant to this field of study.

SYNOPSIS: In this Phase 2 trial, 105 older patients with acute myeloid leukemia who were either treatment-naïve or at first relapse were treated with one of three schedules of oral sapacitabine: 200 mg twice daily for 7 days (group A), 300 mg twice daily for 7 days (group B), or 400 mg twice daily for 3 days each week for 2 weeks (group C). The treatment was well tolerated with 1-year overall survival of 35%, 10%, and 30% in groups A, B, and C, respectively. The 400 mg dose schedule had the best efficacy profile. A platelet count of $\leq 50 \times 10^9$/L and an unfavorable cytogentic risk profile were adverse prognostic factors for 1-year overall survival.

SOURCE: Kantarjian H, et al. Oral sapacitabine for the treatment of acute myeloid leukemia in elderly patients: A randomized phase 2 study. *Lancet Oncol* 2012;13:1096-1104.

Available treatments are inadequate for many elderly patients with acute myeloid leukemia (AML) who are considered to be medically unfit for intensive chemotherapy. At least 80% of patients die within 1 year of diagnosis. The treatment of elderly AML patients is challenging, with poor response rates and high mortality rates following intensive chemotherapy.[1] Findings from cancer registry studies suggest that up to 70% of patients are not offered any treatment other than best supportive care. Recent research trends have emphasized investigational low-intensity and targeted therapies in older patients with AML, hoping to reduce the early mortality and to improve the benefit/risk ratio for long-term survival. Investigational therapies included low-dose cytarabine, arsenic trioxide, gemtuzumab ozogamycin, clofarabine, hypomethylating agents, and others. In this Phase 2 study testing oral sapacitabine, Kantarjian and colleagues recruited 105 elderly AML patients who were previously untreated or at the point of their first relapse. Sapacitabine, 1-(2-C-cyano-2-deoxy-ß-D-arabino-pentafuranosyl)-N4-palmitoylcytosine also known as CYC682, CS-682 is a rationally designed oral prodrug of cytarabine that acts through a dual mechanism. The compound interferes with DNA synthesis causing single-strand DNA breaks and induces arrest of the cell division cycle at G2 phase.[2] Using computer-generated randomization, the researchers assigned the patients to receive one of three schedules of oral sapacitabine: 200 mg

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twice a day for 1 week (group A), 300 mg twice a day for 1 week (group B), or 400 mg twice a day for 3 days each week over a 2-week period (group C). All schedules were administered in 28-day cycles. After 20 patients were treated in a group, an expanded cohort of 20-25 patients were enrolled to that group if at least four patients had achieved complete remission or complete remission with incomplete blood count recovery and if the 30-day mortality was 20% or less. The primary endpoint was 1-year overall survival (OS), analyzed by intent-to-treat in those patients who were assigned to treatment. In all, 60 patients were randomized to treatment. For those patients, 1-year OS was 35% (95% confidence interval [CI], 16-59) in group A, 10% (CI, 2-33) in group B, and 30% (CI, 13-54) in group C. In the expanded cohort of 200 mg, the 1-yr OS was low (10% [CI, 2-33]) when compared to the 400 mg expanded cohort (24% [CI, 10-46]). Within 30 days, 14 (13%) of the 105 patients enrolled died; 27 (26%) died within 60 days. Seven deaths were potentially linked to sapacitabine treatment. The most common grade 3-4 adverse events were anemia, neutropenia, febrile neutropenia, thrombocytopenia, and pneumonia. The most common grade 5 adverse events were pneumonia and sepsis. The most common non-hematological adverse events were gastrointestinal (90% were grade 1-2) which was easily manageable. Fifteen percent in group A, 45% in group B, and 40% in group C required dose reductions because of myelosuppression. A platelet count of $\leq 50 \times 10^9$/L and an unfavorable cytogentic risk profile were adverse prognostic factors for 1-year OS.

COMMENTARY

The current study has shown that oral sapacitabine has encouraging activity in elderly patients with AML. The 200 mg and 400 mg dose schedules had better 1-year OS than did the 300 mg group. The results indicated that the 400 mg dose schedule had the superior efficacy profile in terms of 1-year OS and the number of patients who achieved a complete response. However, all patients who achieved a complete remission in group C had their dose reduced, suggesting that a lower dose of sapacitabine has to be used in future clinical trials, especially if combining with other myelosuppressive agents.

Effective treatment for elderly AML patients has been elusive until the recent trials with targeted therapies, which have shown remarkable activity but their use is restricted to patients with the appropriate target. Hypomethylating agents have also shown encouraging results with low treatment-associated mortality and improved survival despite low rates of complete remissions.[3,4] The literature on randomized trials in AML suggests that improvement of survival in elderly patients might be possible by controlling the disease with low-intensity therapy that has a favorable safety profile rather than by achieving higher complete remission rates with intensive, toxic therapy. Sapacitabine is added to the basket of low-intensity therapies and is shown from the current study to be safe and efficacious. Compared to intensive therapy and to low-dose cytarabine, 30- and 60-day mortality rates were significantly reduced with sapacitabine.[1,5] Another advantage is oral administration of sapacitabine, a feature of importance for the elderly in whom the treatment goal is both improved survival and good quality-of-life. This also allows for combining other low-intensity therapies that might improve outcomes in this poor-prognosis group. Considering that most of the patients in the better tolerated group required dose reductions, a slightly reduced dose of sapacitabine should be considered. We eagerly await the results of one such combination regimen (SEAMLESS STUDY), which is testing sapacitabine (300 mg twice daily for 3 days for 2 weeks) with decitabine. ■

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ABSTRACT & COMMENTARY

Denosumab for Bone Pain in Metastatic Breast Cancer

By Gary R. Shapiro, MD
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Dr. Shapiro reports no financial relationships relevant to this field of study.

SYNOPSIS: **Denosumab is more effective than zoledronic acid at preventing pain in women with advanced breast cancer and bone metastases. Although fewer denosumab-treated patients reported increased analgesic use from no/low use at baseline to strong opioid use, the time to pain improvement and the time to decreased pain interference with daily activities were similar between those using denosumab and zoledronic acid.**

SOURCE: Cleeland CS, et al. Pain outcomes in patients with advanced breast cancer and bone metastases: Results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* 2013;119:832-838.

This randomized, double-blind, double-dummy Phase 3 study was designed to compare the effect of denosumab with zoledronic acid on pain due to breast cancer bone metastases. None of the women in this international study of 2046 women with breast cancer and radiographic evidence of one or more bone metastases had received prior intravenous or oral bisphosphonates for the treatment of bone metastases. Eligible patients were randomized to receive either a monthly subcutaneous injection of denosumab 120 mg and intravenous placebo or subcutaneous placebo and a monthly intravenous infusion of zoledronic acid 4 mg (with appropriate dose adjustments for renal function). Patients completed the Brief Pain Inventory-Short Form at baseline and monthly thereafter. The proportion of patients receiving hormonal treatment or chemotherapy for their breast cancer while on this study was balanced between the denosumab and zoledronic acid treatment groups.

The median time from initial diagnosis of bone metastases to randomization was 2 months, and approximately 33% of patients already had experienced a skeletal related event (SRE) by then. Approximately 53% of women in the denosumab group and 49% in the zoledronic acid group reported no or mild pain at baseline. Patients in both of these groups had worsening pain severity as the study progressed, but fewer women who received denosumab reported a clinically meaningful worsening from their baseline pain: 15% relative difference (5% absolute difference) with an almost 4-month delay (P = 0.002) in the median time to pain worsening to moderate or severe with denosumab (9.7 months) compared with zoledronic acid (5.8 months). Denosumab also delayed the time that it took for pain to interfere with daily activity (decreased pain interference) by 1 month compared with zoledronic acid (16.0 months vs 14.9 months, P = 0.09). The proportion of patients with meaningful improvement in their worst pain score was similar between the treatment groups, ranging from 26% at 1 month to 16% at 18 months for denosumab and from 26% at 1 month to 18% at 18 months for zoledronic acid. The median time to meaningful improvement in the worst pain score also was similar between the treatment groups, 2.7 months for denosumab and 2.8 months for zoledronic acid (P = 0.72). The time to meaningful decrease in pain interference was similar between the groups: denosumab 2.9 months, zoledronic acid 3.2 months (P = 0.92).

Compared to those in the zoledronic acid group, fewer denosumab-treated patients reported increased analgesic use from no/low use at baseline to strong opioid use (relative difference, 20%; absolute difference, 2%). Among patients who had no/low analgesic use at baseline, the median time to strong opioid analgesic use was not reached in the denosumab arm, and was 29.5 months in the zoledronic acid arm (P = 0.27).

COMMENTARY

The majority of women with metastatic breast cancer eventually will develop bone metastases and are at risk for SRE such as pain, spinal cord compression, pathologic fractures, and hypercalcemia. Randomized clinical trials have demonstrated that bisphosphonates reduce SRE and pain associated with bone metastases,[1] and that zoledronic acid may be superior to pamidronate in those with lytic breast cancer bone metastases.[2]

In 2010, Stopeck et al reported that denosumab was superior to zoledronic acid in preventing SREs in patients with breast cancer and bone metastases, and that women who are candidates for bisphosphonate therapy also should be considered for treatment with denosumab.[3] Using data from that study, Cleeland et al examined the effect of these agents on pain outcomes: pain severity, analgesic use, and the degree to which pain interferes with common dimensions of feeling and function (pain interference). This is the first study to analyze how these agents affect the length of time until significant pain develops.

Cleeland et al found that denosumab was more effective at extending the time to significant increases in pain and pain-related functional interference as well as the time to first use of strong opioid analgesics compared with zoledronic acid, particularly among patients who had no or mild pain at baseline. Both agents had comparable levels of pain palliation.

Though both zoledronic acid and denosumab are extremely well tolerated, they have somewhat different side effect profiles. Hypocalcemia occurs more frequently with denosumab, and zoledronic acid causes more kidney-related problems and acute phase reactions. Osteonecrosis of the jaw is an infrequent risk of both (1-2%). The long-term risks of denosumab and the optimal duration of treatment are not known.

The subcutaneous route of denosumab administration is certainly an advantage over the zoledronic acid intravenous route, but its main benefit over zoledronic acid is that it delays the onset of cancer pain and pain-related functional interference. Consequently, these women, especially those with no or only mild pain at baseline, enjoy a prolonged period of pain control without suffering the side effects of the stronger opioid analgesics. One hopes that these important quality-of-life benefits also apply to those with bone metastases from other tumor types, but additional studies are needed before extrapolating these findings beyond breast cancer. ■

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ABSTRACT & COMMENTARY

Sunitinib in Older Renal Cell Carcinoma Patients

By William B. Ershler, MD

SYNOPSIS: In a six-site Italian retrospective analysis, treatment of elderly patients with metastatic renal cell carcinoma with sunitinib was shown to be effective but associated with significant toxicity. Although only applied to a subset, pretreatment comprehensive geriatric assessment did not offer predictive value with regard to severe toxicity or efficacy.

SOURCE: Brunello A, et al. Safety and activity of sunitinib in elderly patients (≥ 70 years) with metastatic renal cell carcinoma: A multicenter study. *Ann Oncol* 2013;24:329-336.

Sunitinib is a tyrosine-kinase inhibitor (TKI) active at vascular endothelial and platelet-derived growth factor receptors.[1] Its use has been shown to significantly prolong progression-free survival (PFS) and overall survival (OS) in patients with metastatic renal cell carcinoma (mRCC).[2] The drug, however, is not without side effects including hypertension, fatigue, diarrhea, hypothyroidism, and hand foot syndrome,[3] and its safety and efficacy in elderly patients has yet to be established. This is not merely an academic question as the median age at diagnosis is approximately 65 years,[4] and an increasing percentage of patients present with comorbidities and/or functional impairments that may well lead to a higher risk of intolerance to treatment.

To address this, Brunello and colleagues examined medical records of elderly mRCC patients treated with sunitinib at six Italian centers. Their goal was to assess safety (primary objective), efficacy, and the correlation of toxicity with comprehensive geriatric assessment (CGA) (secondary objectives).

Their analysis included 68 elderly treated patients (median age of 74 years). CGA had been carried out in 34 patients prior to treatment (41% fit, 41% vulnerable, and 18.5% frail). A dose reduction from 60 mg to 37.5 mg was made up front or soon after the first cycle in 69.1%. More frequent toxic

effects were fatigue (80.9%), mucositis (61.8%), and hypertension (58.8%). Cardiac events occurred in nine patients. In 10 patients, therapy was interrupted early due to rapidly progressive disease (10.3%) or severe toxicity (4.4%; 1 cardiac failure, 1 fatigue, 1 febrile neutropenia). At a median follow-up of 27.1 months, the median OS was 18.3 months and the median PFS was 13.6 months. Correlation was not found between frailty at CGA with severe toxicity nor with response.

COMMENTARY

The introduction of targeted therapies has dramatically changed the treatment approach for metastatic renal cell carcinoma (mRCC). However, as is often the case, there remain few data to balance efficacy vs toxicity when prescribing for older patients, particularly for those who are frail. This is primarily because pivotal clinical trials in drug development typically enroll younger patients with less comorbidity and functional impairment. Yet a subset analysis of older patients enrolled on pivotal trials of selected targeted therapies for mRCC suggest similar rates of favorable response.[5] This, of course, is also subject to bias because elderly patients enrolled on trial may not represent the typical frail patient with comorbidities.

The current report is important, for it details the age-related toxicity profile for one such targeted therapy (sunitinib). Although the numbers were small, pretreatment CGA was shown not to offer predictive value with regard to either toxicity or efficacy. This disappointing finding would suggest that much work needs to be done on refining the CGA. It is possible that an instrument proven useful for one set of circumstances (e.g., for predicting tolerability of chemotherapeutic approaches) might be different for another (e.g., tyrosine kinase inhibitors). It remains a major goal in geriatric oncology to develop a feasible assessment instrument on which appropriate treatments can be prescribed, enriching for those who are likely to respond and reducing toxicities for those who are not.

One may conclude from the current report that sunitinib is effective in at least some elderly mRCC patients, although early treatment interruptions and dose modifications were common. A prospective clinical trial in which treatment initiation at a reduced dose with escalation as tolerated might be a reasonable next step. ■

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ABSTRACT & COMMENTARY

Use of Sorafenib in Advanced HCC Patients with Child-Pugh Class B Liver Dysfunction

By William B. Ershler, MD

SYNOPSIS: Early pivotal trials demonstrating the efficacy of sorafenib for patients with advanced hepatocellular cancer included primarily those with minimal liver dysfunction (Child-Pugh [CP] class A). The current Phase 2 study examined sorafenib treatment in both CP class A and B patients. Those with CP class B liver dysfunction were shown to tolerate sorafenib but treatment outcomes remained less satisfactory than for CP class A patients.

SOURCE: Pressiani T, et al. Sorafenib in patients with Child-Pugh class A and B advanced hepatocellular carcinoma: A prospective feasibility analysis. *Ann Oncol* 2013;24:406-411.

Hepatocellular cancer (HCC) is among the most common cancers worldwide and is becoming more prevalent in western countries.[1] In 50% or more of cases, the disease presents at an advanced stage for which systemic therapies have been of limited demonstrable value. Sorafenib, a small molecule multikinase inhibitor,[2] was the first systemic agent to prolong survival in patients with advanced HCC, as demonstrated in two Phase 3 trials,[3,4] and now represents the standard systemic treatment for such patients.[5-7] In patients with advanced HCC but with only modest pre-existing liver injury (Child Pugh [CP] class A) sorafenib has shown survival benefits.[3,4] However, the question remains of whether sorafenib can be administered safely and with similar efficacy for advanced HCC patients with more advanced liver dysfunction (CP class B).

To address this, Pressiani and colleagues conducted an open-label, multicenter, Phase 2 trial throughout Italy. This was a dual-phase trial; the first phase was designed to prospectively investigate the feasibility of sorafenib treatment in patients with poorer (CP class B) compared with better (CP class A) liver function.

During the first phase, all patients received continuous oral treatment with sorafenib 400 mg twice daily until radiological progression (as defined by RECIST), symptomatic progression or deterioration of PS, unacceptable toxic effects, or patient withdrawal. Treatment interruptions and dose reductions were permitted for drug-related adverse events (AEs). The second phase of the trial (reported at ASCO 2012 Gastrointestinal Cancers Symposium[8]) was initiated on radiological disease progression. Patients were randomized to sorafenib dose escalation (600 mg twice daily) or best supportive care.

For this study, a consecutive, prospective series of 300 patients with CP class A or B HCC were enrolled to determine safety of treatment and assess survival in the context of liver function (CP class A or B). Patients received oral sorafenib 800 mg daily.

Overall progression-free survival (PFS), time to progression (TTP), and overall survival (OS) were 3.9, 4.1, and 9.1 months, respectively. For patients with CP class A vs B status, PFS was 4.3 vs 2.1 months, TTP was 4.2 vs 3.8 months, and OS was 10.0 vs 3.8 months. Extrahepatic spread was associated with worse outcomes but taken together with CP class, liver function played a greater role in reducing survival. Adverse events for the two CP groups were similar.

COMMENTARY

It is well established that for patients with advanced HCC, preexisting liver dysfunction (CP class B) predicts poorer outcomes,[9] and it remained to be determined whether systemic treatment with sorafenib would be tolerable and or effective in this situation. Although instructive, the current descriptive analysis was not specifically designed to compare outcomes in patients according to CP class. However, a good number of CP class B patients were treated and the data would suggest the drug can be administered safely and on the same schedule as for those with less compromised liver function. The overall value of sorafenib for CP class B HCC patients in terms of TTP, PFS, and OS remains to be established. ■

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ABSTRACT & COMMENTARY

Laparoscopy vs Laparotomy in Early Uterine Cancer: We Still Don't Know

By Robert L. Coleman, MD

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Dr. Coleman reports no financial relationships relevant to this field of study.

This article originally appeared in the April 2013 issue of *OB/GYN Clinical Alert*.

SYNOPSIS: LAP2 was a randomized, Phase 3 trial to evaluate and compare the modality of surgical staging (laparoscopy vs laparotomy) in endometrial cancer. The primary endpoint was assessing non-inferiority of laparoscopy relative to laparotomy on recurrence-free survival. Although the estimated recurrence rates and 5-year overall survival were nearly identical between the arms, the noninferiority objective (i.e., the statistical proof that the laparoscopic approach is not inferior to laparotomy in terms of overall survival) was not met.

SOURCE: Walker JL, et al. Recurrence and survival after random assignment to laparoscopy versus laparotomy for comprehensive surgical staging of uterine cancer: Gynecologic Oncology Group LAP2 study. *J Clin Oncol* 2012;30:695-700.

LAP2 was a Phase 3 clinical trial to assess the noninferiority of laparoscopy compared with laparotomy for recurrence of uterine cancer after surgical staging. Eligible patients had clinical stage I-IIA disease, were histologically either adenocarcinoma or sarcoma, and were randomly allocated (2 to 1) to laparoscopy (n = 1696) or laparotomy (n = 920). Patients in both arms were to have a standard surgical staging: hysterectomy, salpingo-oophorectomy, pelvic cytology, and pelvic and paraortic lymphadenectomy. The primary endpoint was noninferiority of recurrence-free interval defined as no more than a 40% increase in the risk of recurrence with laparoscopy compared with laparotomy (upper limit hazard ratio: 1.4).

Over a median follow-up of 59 months, there were 309 recurrences (210 laparoscopy, 99 laparotomy) and 350 deaths (229 laparoscopy, 121 laparotomy). The estimated 3-year recurrence rates were 11.4% and 10.2% for laparoscopy and laparotomy, respectively (90% lower bound, -1.28; 95% upper bound, 4.0). The estimated hazard ratio for laparoscopy relative to laparotomy was 1.14 (90% lower bound, 0.92; 95% upper bound, 1.46), falling short of the protocol-specified definition of noninferiority. The estimated 5-year overall survival was almost identical in both arms at 89.8%. Multivariate analysis identified age, surgical stage, cell type, myometrial invasion, and lympho-vascular invasion as independent factors influencing recurrence; however, there was no difference by surgical approach among these factors. The authors concluded that the study, which previously had reported the superiority of laparoscopic surgical management on short-term safety and length-of-stay endpoints, did not meet its noninferiority endpoint. However, the quantified risks were small, providing accurate information for decision making for women with uterine cancer.

COMMENTARY

The standard operative procedure for patients with primary endometrial cancer is hysterectomy, bilateral salpingoophorectomy, and surgical staging including assessment of the pelvic and paraortic lymph nodes. Traditionally, this has been done via exploratory laparotomy (ceiliotomy), where access to pelvic and abdominal areas is generally assured. However, more than 20 years ago, each of the critical steps in surgical staging for this disease was found to be feasible via minimally invasive surgical (MIS) techniques.[1,2] Over these past 2 decades, the standard approach has increasingly been replaced by laparoscopy and robotic endoscopy.[3] Critics argued that compromised procedures due to patient (e.g., body habitus limiting exposure), surgeon (e.g., loss of tactile feedback and limited capability to assess the high paraortic nodes), and technical (e.g., potential for aerosolization of tumor cells by CO2) factors would increase the likelihood of recurrence and lower survival in patients undergoing the MIS approach.[4-7] LAP2 initially was launched to assess morbidity and mortality of MIS in endometrial cancer staging, but was amended in 2001 to also address the noninferiority of MIS relative to laparotomy. The trial was designed with a 2:1 randomization and established confidence limits for noninferiority based on an anticipated recurrence rate in the laparotomy arm of 15%. The statistics are important in understanding the "accurate" interpretation of the study. As strictly demonstrated, the lower limit of the confidence interval assessing inferiority crosses 1.0. This would, under normal circumstances, reject the null hypothesis of inferiority for MIS, concluding that there was not a substantial increase in recurrence for the MIS approach.

[Minimally invasive surgical approaches are preferred in uterine cancer patients, particularly in those with high body mass index, as operative and postoperative morbidity can be substantially ameliorated.]

However, because the observed recurrence rate was substantially lower than anticipated, the upper limit of this same confidence interval crosses 1.4, which under the initial assumptions would have rejected the alternate hypothesis (that is, MIS is noninferior to laparotomy). So in an argument, both conclusions could be supported, and strictly speaking, the study's conclusions are ambiguous. Fortunately, the actual differences in recurrence rate, site of recurrence, 3-year recurrence risk, 5-year overall survival, and just about every other metric are nominal and "practically" identical. This colossal effort on behalf of the Gynecologic Oncology Group is to be commended as the history of completing this trial with all of the excitement for MIS at the time was a challenge. Currently, the MIS approach is preferred particularly in patients who have very high body mass index, as the operative and postoperative morbidity can be substantially ameliorated. However, when the surgical output is compromised by the approach, it cannot be justified. ■

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- describe new advances in the field of oncology.

Continuing Education Questions

1. What adverse prognostic factor was associated with 30-day mortality with oral sapacitabine in elderly acute myeloid leukemia patients in the study by Kantarjian et al?

a. White blood cell count of $\geq 10 \times 10^9$/L
b. Platelet count of $\leq 50 \times 10^9$/L
c. Intermediate risk cytogenetic profile
d. Bone marrow blast cells of ≥ 50%

2. Which of the following is an option for women with breast cancer bone metastases?

a. Zoledronic acid
b. Denosumab
c. Both A and B
d. Neither A nor B

3. In the subset of elderly renal cell cancer patients treated with sunitinib for whom comprehensive geriatric assessment was performed, the assessment proved useful in predicting:

a. overall survival.
b. incidence of treatment-related toxicity.
c. early cancer-related death.
d. All of the above
e. None of the above

4. When considering treatment for patients with advanced hepatocellular carcinoma, the data from the Pressiani study would indicate:

a. patients with CP class B will tolerate treatment as well and are likely to achieve similar PFS and OS as those with CP class A.
b. patients with CP class B will tolerate treatment as well as those with CP class A, but outcomes in terms of PFS and OS do not reach those achieved by those with CP class A.
c. patients with CP class B exhibit intolerance to sorafenib treatment requiring dose reductions and delays.
d. patients with CP class B had less sorafenib toxicity and greater improvements in PFS than observed in CP class A patients.

5. Which of the following factors is responsible for the ambiguous noninferiority conclusion of the study by Walker et al?

a. The sample size
b. The inclusion of sarcoma
c. The inaccurate clinical staging procedure
d. The lower observed recurrence rate
e. The rate of unexpected pre-progression deaths

[IN FUTURE ISSUES]

Explaining aromatase-inhibitor joint pain

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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A Relationship Between Nocturia and Hypertension

Source: Feldstein CA. *J Am Soc Hypertens* 2013;7:75-84.

Nocturia could easily be misconstrued as a "nuisance" symptom since, after all, nobody dies from nocturia … or do they? Indeed, urinary frequency and nocturia have been associated with greater risk for nocturnal falls and hip fracture; hence, nocturia can be much more than just a nuisance.

Clinicians are used to identifying nocturia as a symptom associated with benign prostatic hyperplasia, overactive bladder, uncontrolled diabetes, uncontrolled congestive heart failure, use of diuretics, and (less commonly) interstitial cystitis. What is only minimally recognized, however, is the emerging observation that hypertension is associated with nocturia.

Several plausible mechanisms can explain the nocturia/hypertension relationship: hypertension-induced alterations in glomerular filtration or tubular transport, activation of atrial natriuretic peptide from ventricular wall stress induced by hypertension, and resetting of the pressure-natriuresis relationship in the kidney, to name a few.

Feldstein indicates that the prevalence of nocturia in untreated hypertension patients may be as high as 33%. Since nocturia can be both a burdensome symptom and lead to significant morbidity (and mortality), clinicians may wish to specifically inquire about nocturia when encountering hypertension patients. ■

Peripheral Artery Disease: Helping Patients to Walk the Walk

Source: Ahimastos AA, et al. *JAMA* 2013; 309:453-460.

Currently available treatments for peripheral artery disease (PAD) are only modestly effective. PAD portends increased risk of cardiovascular disease; hence, most PAD patients should be receiving pharmacotherapy with a statin and an antiplatelet agent (usually clopidogrel).

Because one of the quality-of-life limiting factors in advanced PAD is disease-mediated diminution in walking distance and walking time, incorporation of pharmacotherapy to improve these limitations is also considered important. Unfortunately, the two FDA-approved treatments (pentoxifylline and cilostazol) for symptoms of PAD provide only a modest increase in walking distance (25% or less). Smoking cessation and exercise advice remain critically important, but are too often not heeded.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that has been used in numerous major clinical trials, including the HOPE trial, ONTARGET trial, REIN trial, and others. Use of ramipril is usually predicated on 1) its ability to lower blood pressure, 2) its ability to improve outcomes in congestive heart failure, or 3) its ability to improve albuminuria.

Based on results seen in a small pilot trial that suggested favorable results of ramipril on treadmill time in subjects with PAD, Ahimastos et al performed a larger randomized clinical trial (n = 212).

At the conclusion of the 6-month trial of ramipril 10 mg/day vs placebo, pain-free walking time had increased by more than 50% in the ramipril group, but only 10% in the placebo group.

Although the mechanism for improved function is speculative, it has been noted that ACE inhibitors increase skeletal muscle blood flow; indeed, this has been the mechanism to which improved insulin sensitivity in diabetics has been attributed. Ramipril may offer a new avenue to improve functionality in patients with PAD. ■

Long-Term Functional Outcomes After Localized Prostate Cancer Treatment

Source: Resnick MJ, et al. *N Engl J Med* 2013;368:436-445.

When prostate cancer is localized, either radical prostatectomy (RPT) or external beam radiation (EBR) can often be curative. The adverse effect profile of these two interventions, however, may be meaningfully different and such differences might also be time-dependent.

Resnick et al studied men (n = 1164) from the Prostate Cancer Outcomes Study who had been enrolled between the ages of 55-74 and had localized prostate cancer. More than 80% of the men had a Gleason score of 7 or less. The prevalence of urinary incontinence (UI) and erectile dysfunction (ED) were compared among these men at years 2, 5, and 15.

Prostatectomy subjects were five to six times more likely to have incontinence at

2 years and 5 years than EBR subjects. Similar disadvantage was seen in the prevalence of ED (two- to four-fold increased incidence in the RPT group). At the 15-year conclusion of their observations, no differences between groups remained. However, one would anticipate, for instance, a substantial incremental increase in ED as men age *with or without intervention*; hence, the fact that between-group differences are eliminated by 15 years provides little solace for the men who suffer the adverse effects in the interim! ■

The Word 'GPR40 Modulator' May Soon be Entering Our Vocabulary

Source: Basu A, et al. *Diabetes Care* 2013;36:185-187.

The search for safe and effective agents to treat type 2 diabetes (DM2) continues, with hypoglycemia often being a limiting adverse effect of otherwise highly efficacious agents.

It has been observed that free fatty acids (FFA) play a role in glucose homeostasis, although the story line is complex. Acutely, elevations of FFA *stimulate* beta cell secretion of insulin. *Chronic* FFA elevations result in an impaired insulin response to high glucose levels, a phenomenon known as lipotoxicity.

The mechanism by which FFA impacts insulin secretion has been elegantly worked out and includes the G-protein-coupled receptor (GPR40). Because GPR is involved not only in insulin secretion, but also plays a role in obesity and dyslipidemia, its potential as a multimodal intervention has looked promising.

Studies in humans have shown that GPR40 agonists live up to the expectation that they lower glucose, with a very low risk of hypoglycemia. For instance, a head-to-head comparison with the sulfonylurea glimepiride found hypoglycemic episodes to be six-fold lower with the GRP40 agonist.

In an era of a burgeoning population of DM2 patients, we look forward to the addition of pharmacotherapies that safely complement our current options. ■

A More Effective Regimen for *H. pylori* Eradication

Source: Liou JM, et al. *Lancet* 2013;381: 205-213.

In the United States, peptic ulcer disease is caused primarily by two culprits: nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* (and their combination). Evolution of pharmacotherapy for *H. pylori* currently employs combinations of amoxicillin (AMOX), metronidazole (METR), clarithromycin (CLAR), and a proton pump inhibitor (PPI). Unfortunately, over time *H. pylori* eradication rates with such regimens have fallen to as low as 80% or less. Is there a better way?

Liou at al randomized *H. pylori*-positive Taiwanese adults (n = 900) to one of three regimens — 1) Sequential 10 days: PPI + AMOX for 5 days followed by PPI + CLAR + METR for 5 days; 2) Sequential 14 days: PPI + AMOX for 7 days followed by PPI + CLAR + METR for 7 days; or 3) Standard 14 days: PPI + AMOX + CLAR for 14 days. The PPI used in this clinical trial was lansoprazole.

Adverse effect profiles of the three regimens were similar. Eradication rates were statistically significantly higher using sequential regimens (10 days = 87%, 14 days = 91%) than in standard regimens (82%).

Reflecting an increased recognition of problematic CLAR resistance at the end of the initial comparison trial, treatment failures from each regimen were assigned to receive an additional 14-day sequential course of treatment in which levofloxacin was substituted for CLAR. Eradication rates from this "rescue" population (regardless of which initial regimen they had received) were 80%.

Based on this large dataset, the authors suggest that sequential treatment regimens should become first line. ■

Uric Acid: How Much of a Bad Guy?

Source: Rosendorff C, et al. *J Clin Hypertens* 2013;15:5-6.

Uric acid (URA) has become the object of intense scrutiny of late, with more than its share of accusations linking it to hypertension and heart disease. The relationship between URA and gout is incontrovertible, though not necessarily universal. That is, in persons who develop gout, risk of future attacks is definitely related to absolute URA plasma levels. However, among persons without gout, elevations of URA appear to be well tolerated without evident toxicity in most: In asymptomatic adults with URA levels > 9.0 mg/dL, only about 5% per year go on to manifest acute gout.

The association of URA with hypertension, myocardial infarction, and even congestive heart failure is acknowledged. Whether this relationship is *causal*, and if a causal relationship is determined, whether lowering of URA will be beneficial remains to be determined. Remember the enthusiasm attendant to the recognition that homocysteine was associated with cardiovascular disease, heightened by the assurance that lowering homocysteine was simple and safe (B vitamins and folate), soon thereafter torpedoed by the interventional trials that failed to show improved outcomes in subjects whose homocysteine levels were reduced?

Despite the growing enthusiasm for criminalizing URA, we still do not have a large randomized, controlled trial indicating that modulation of URA improves hard endpoints. Until then, since all medications that reduce URA have their own bundle of potential misadventure to consider, we should watch and wait. ■

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■